UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

JANSSEN PHARMACEUTICA N.V., and JANSSEN PHARMACEUTICA PRODUCTS, L.P.	:	
Plaintiffs,	:	CIVIL ACTION NO. 03-6220 (JCL)
v.	:	
MYLAN PHARMACEUTICALS., INC.	:	
Defendants.	:	
JANSSEN PHARMACEUTICA N.V., and JANSSEN PHARMACEUTICA PRODUCTS, L.P.	:	
Plaintiffs,	:	CIVIL ACTION NO. 03-6185 (JCL)
v.	:	**OPINION**
DR. REDDY'S LABORATORIES, LTD., and DR. REDDY'S LABORATORIES, INC.	:	
Defendants.	:	

LIFLAND, District Judge

I. Introduction

Plaintiffs, Janssen Pharmaceutica, N.V., a Belgian corporation, and its New

Jersey-based subsidiary, Janssen Pharmaceutica, L.P. (collectively "Janssen"), are the inventors and producers of risperidone, the active ingredient in Janssen's successful drug for the treatment of schizophrenia, Risperdal. It is perhaps an understatement to describe Risperdal as merely "successful." The drug has been described by the American Chemical Society as "a standard in the treatment of psychosis, revolutionizing anti-psychotic treatments." Pl.'s Ex. ("PX") 309. In 2005 alone, Risperdal accounted for over $3 billion in worldwide sales for Janssen's parent company, Johnson & Johnson. Vergis Tr. 78:9-16.

Defendants, Mylan Pharmaceuticals, Inc. ("Mylan"), a West Virginia corporation, Dr. Reddy's Laboratories, Ltd., an Indian corporation, and its New Jersey-based subsidiary, Dr. Reddy's Laboratories, Inc. (collectively, "DRL"), are drug manufacturers seeking to market a generic version of risperidone. Janssen filed this suit claiming infringement of its U.S. Patent No. 4,804,663 ("the '663 patent"), which claims risperidone, among other chemical compounds. Mylan and DRL concede they have infringed the '663 patent; they counter, however, that the '663 patent is invalid due to obviousness, and alternatively, Mylan argues that the '663 patent is unenforceable due to Janssen's alleged inequitable conduct.

The parties tried the case before the Court from June 28, 2006 through June 30, 2006 and on July 5, 2006. Thereafter, they submitted proposed findings of fact

and conclusions of law. The parties' submissions and the record evidence have been carefully considered. For the reasons set forth below,[1] the Court finds that Mylan and DRL have failed to prove by clear and convincing evidence that the '663 patent is obvious under 35 U.S.C. § 103(a), and that Mylan has failed to prove by clear and convincing evidence that Janssen engaged in inequitable conduct. Thus, the '663 patent is neither invalid nor unenforceable, and as a result, Mylan and DRL have infringed that patent under 35 U.S.C. § 271(e)(2).

II. Background

A. The '663 Patent

On February 14, 1989, the United States Patent and Trademark Office ("PTO") issued the '663 patent to its inventors Ludo E.J. Kennis and Jan Vandenberk and assignee, Janssen. PX 1. The '663 patent originated from a patent application filed with the PTO on March 27, 1985. Stipulations of Fact ("SF") 14-15; PX 1.

The '663 patent's 18 claims encompass compounds "having useful antipsychotic properties and being useful in the treatment of a variety of complaints in which serotonin release is of predominant importance." PX 1.

[1] This opinion shall constitute the Court's findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a).

Among those compounds are risperidone and compound 11, which are included in each of the patent's 18 claims.[2] SF-17. There is no claim in the '663 patent in which risperidone is the only compound. PX 1; Wolff Tr. 546:1-10.

The compounds claimed in the '663 patent were the result of Janssen's efforts to invent an effective antipsychotic drug, with few side effects, for the treatment of Schizophrenia. Tamminga Tr. 53:4-22.

B. Schizophrenia

Schizophrenia is a debilitating disease of the brain characterized by hallucinations, delusions and other symptoms that impair a person's capacity for thought, attention, memory, emotion and social functioning. Tamminga Tr. 46:19-47:1. Despite much research, the cause, mechanism, and etiology of the disease remain unknown. Tamminga Tr. 47:2-3.

People who suffer from schizophrenia exhibit a wide array of symptoms that can be classified into three major categories: positive symptoms, negative symptoms, and cognitive symptoms. Tamminga Tr. 47:4-7.

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[2] In the '663 patent, the chemical name for Risperidone is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro- 2-methyl-4H-pyrido[1,2-a]-pyrimidin-4-one; the chemical name for Compound 11 is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-2-methyl-4H-pyrido[1, 2-a]pyrimidin-4-one. Defs.' Ex. ("DX") 1.

Positive symptoms include extreme hallucinations and paranoid delusions. Hallucinations are auditory, visual or both. Schizophrenics do not just hear voices in their mind, "they believe that there are people actually talking to them." Tamminga Tr. 47:8-16. In addition, schizophrenics believe in the false realities created by their delusions, sometimes causing the delusions to take over their lives. Id. at 47:17-18.

Negative symptoms include the complete loss of all emotion and lack of spontaneous thought, both of which "result in a loss of social skills and really an entire loss of social functioning." Tamminga Tr. 47:19-24.

Cognitive symptoms include the impairment of memory and attention. These cognitive deficits cause schizophrenics to become unable to use information and to have great difficulty making decisions. Tamminga Tr. 47:25-48:4.

These symptoms can entirely take over the lives of persons with schizophrenia, preventing them from working or developing social networks. Less than 20 percent of schizophrenics have jobs, less than 15 percent ever marry, and approximately 10 percent eventually commit suicide. Tamminga Tr. 48:5-15.

C. Early Treatments

Schizophrenia is a disease as old as mankind. For most of that time, there were no effective medical treatments. The only option was compassionate care,

placing schizophrenics into protected environments such as government hospitals that quickly became overcrowded. But compassionate care did nothing to treat the symptoms and the patients did not get better. Tamminga Tr. 48:18-49:2.

Beginning in the 1930s, doctors attempted medical treatments. These treatments included induced fever, electroconvulsive shock therapy and frontal lobotomy. None of these attempts to treat the disease was effective. To the contrary, these treatments could even worsen the symptoms of schizophrenia. Tamminga Tr. 49:3-12.

D. First Generation, "Typical" Antipsychotic Drugs

The lack of effective treatment options continued into the 1950s. Then, for the first time, doctors developed an antipsychotic drug to treat schizophrenia, called chlorpromazine. Tamminga Tr. 49:13-18. The discovery that chlorpromazine could treat some symptoms of schizophrenia was accidental. Physicians were testing chlorpromazine as a sedative when they noticed that chlorpromazine significantly reduced the hallucinations and delusions of their schizophrenic patients. Tamminga Tr. 49:19-25.

As the first pharmaceutical treatment for schizophrenia, chlorpromazine was rapidly adopted for use throughout the medical community. Pharmaceutical companies quickly began searching for similar drugs. This led to the development

of new antipsychotics such as Janssen's haloperidol, marketed under the trade name, Haldol. Chlorpromazine, haloperidol, and other similar drugs became known as first generation, or typical, antipsychotics. Tamminga Tr. 50:12-16, 21-25.

While chlorpromazine and the other typical antipsychotics were an improvement over compassionate care and the early ineffective treatments, they were not perfect. A typical antipsychotic improved the positive symptoms of schizophrenia, but it had no effect on the negative or cognitive symptoms that severely impaired the emotions, thoughts, and social functioning of schizophrenics. In fact, in some cases a typical antipsychotic could even worsen these symptoms. Tamminga Tr. 50:1-3.

More significantly, even when typical antipsychotics were successful at treating the positive symptoms of schizophrenia, they had many unwanted and serious side effects, including sedation, cardiac side effects, and motor side effects. The motor-related side effects were the largest drawback. Tamminga Tr. 51:1-5.

For example, typical antipsychotics caused extrapyramidal symptoms ("EPS") that caused patients to experience rigidity and tremors similar to those of Parkinson's disease. The rigidity and tremors brought on by EPS were always

uncomfortable and often painful. EPS symptoms tended to cease when a patient stopped taking the medication. Tamminga Tr. 51:6-52:2.

Even worse, EPS symptoms could also gradually develop into a more serious motor syndrome called "tardive dyskinesia" ("TD"), characterized by motor difficulties such as, repetitive, involuntary, and purposeless movements. Unlike EPS, tardive dyskinesia was frequently irreversible even after the medication was discontinued. Tamminga Tr. 51:13-23.

These side effects had significant repercussions in the treatment of schizophrenia. Not surprisingly, patients disliked these motor side effects so much that they sometimes stopped taking their medication altogether. Tamminga Tr. 52:3-5.

E. Second Generation, "Atypical" Antipsychotic Drugs

In the 1960s, scientists' search for an improved antipsychotic resulted in the development of the first second generation or "atypical" antipsychotic, clozapine. Clozapine was introduced in the 1960s in Europe. Unlike the typical antipsychotics, clozapine had reduced motor side effects. Tamminga Tr. 52:6-9, 52:25-53:1.

Soon after clozapine was introduced, however, researchers discovered that while it had reduced motor side effects, it had a significant toxicity issue. It was

found that clozapine could cause agranulocytosis, a sometimes deadly blood disorder. Due to its toxicity, the Food and Drug Administration ("FDA") did not approve clozapine in the United States until 1990. And even then, it was not approved for general use; its approval was limited to use only with treatment-resistant patients. Tamminga Tr. 52:10-24.

Despite this drawback, the discovery of clozapine demonstrated that it was possible to treat the positive symptoms of schizophrenia without serious motor side effects. It gave the medical community renewed hope for developing improved antipsychotic drugs. Tamminga Tr. 53:2-8. For that reason, clozapine became the focus of researchers looking for new drugs that would incorporate clozapine's improvements without its toxicity. Strupczewski Dep. (11/16/2004) Tr. 82:4-12. For example, both Eli Lilly and Sandoz spent years on research programs to modify clozapine to create a drug that would retain clozapine's benefits and eliminate its toxic effect. Meltzer Tr. 250:3-17; Tamminga Tr. 53:2-8.

F. Risperidone

Janssen was one of the companies attempting to develop a safe atypical antipsychotic. Following years of research and the testing of many potential compounds, two Janssen scientists, Kennis and Vandenberk, discovered

risperidone. When approved by the FDA, risperidone became the first atypical antipsychotic available for general use that effectively treated symptoms with reduced side effects. Risperidone, sold by Janssen under the trademark Risperdal, was approved by the FDA in late 1993 and was first sold in the United States in 1994. Tamminga Tr. 53:9-13; Vergis Tr. 76:6-7, 13-15, 76:24-77:5.

Risperidone was a major advance over the typical antipsychotic drugs. Tamminga Tr. 55:19-56:5. Like the typical antipsychotics, risperidone has a potent effect in treating the positive symptoms of schizophrenia. However, unlike the typical antipsychotics, risperidone also improves the negative and cognitive symptoms of schizophrenia. Moreover, risperidone also has an extremely low side effect profile, with reduced EPS and almost no TD. Tamminga Tr. 53:14-22, 55:19-56:5.

Risperdal had a revolutionary impact on the treatment of schizophrenia. Once risperidone entered the market, the medical community "set aside" the typical antipsychotics. Tamminga Tr. 55:19-25.

G. Mylan & DRL's Abbreviated New Drug Applications

Following Janssen's success with Risperdal, generic manufacturers began filing Abbreviated New Drug Applications ("ANDA") with the FDA under the Hatch-Waxman Act, 28 U.S.C. § 355(j)(1), seeking approval to sell generic

risperidone products. Most of those companies chose not to challenge Janssen's '663 patent and included a "paragraph III" certification under 28 U.S.C. § 355(j)(2)(A)(vii)(III), indicating that the FDA should not approve their applications until after the expiration of the '663 patent. Vergis Tr. 82:9-13; PX 75, PX 76, PX 77, PX 78, PX 85; PX 396.

On November 29, 2001, Mylan submitted an ANDA (No. 76-288) to the FDA seeking approval to market a generic risperidone tablet in various doses. Initially, Mylan also chose not to challenge the '663 patent by including a paragraph III certification with its ANDA. SF 21.

On October 24, 2003, DRL submitted an ANDA (No. 76-879) to the FDA also seeking to sell a generic version of risperidone. SF-27. DRL's ANDA, however, contained a "paragraph IV" certification pursuant to 28 U.S.C. § 355(j)(2)(A)(vii)(IV), challenging the validity of the '663 patent.[3] SF 29. On November 19, 2003, Mylan followed DRL's lead and amended its ANDA (No. 76-288) to include a paragraph IV certification. SF-23. Both Defendants informed Janssen of its paragraph IV certifications shortly thereafter. SF 24, 29.

H. <u>The Current Litigation</u>

[3] DRL twice amended its ANDA to include different doses and variations of a generic risperidone.

On December 30, 2003, Janssen filed separate patent infringement actions against Mylan (Civil No. 03-6220) and DRL (Civil No. 03-6185) under 35 U.S.C. § 271(e)(2).[4] On March 8, 2004, the two actions were consolidated for discovery and pre-trial purposes. Two additional actions filed by Janssen against DRL (Civil Nos. 05-0884, 5326) based on the filing of additional paragraph IV certifications for different forms of risperidone were consolidated with No. 03-6185 on March 9, 2006.

In February 2004, Mylan and DRL filed separate answers. Both Defendants asserted an affirmative defense claiming that the '663 patent is invalid for obviousness under 35 U.S.C. § 103(a). Both Defendants also asserted a counterclaim seeking a declaration of invalidity.

On June 7, 2006, Mylan amended its answer to include the additional affirmative defense that the '663 patent is unenforceable due to Janssen's alleged inequitable conduct. Mylan also seeks a declaratory judgment to that effect. DRL did not join Mylan in asserting this defense and counterclaim.

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[4] Upon receiving notice of an applicant's paragraph IV certification, 35 U.S.C. § 271(e)(2) permits the patent holder to immediately bring an action in a U.S. District Court for a determination that the application infringes the patent. See, e.g., SmithKline Beecham Corp. v. Apotex Corp., 439 F.3d 1312, 1314 (Fed. Cir. 2006).

I. Jurisdiction, Venue and Applicable Law

This Court has subject matter jurisdiction over Janssen's patent infringement claims and Mylan and DRL's counterclaims pursuant to 28 U.S.C. §§ 1331 and 1338(a). Defendants have waived any objections to this Court's exercise of personal jurisdiction, SF 11, and venue is proper under 28 U.S.C. §§ 1391(b)(1) and (c), and 1400(b).

Because this action arises under the patent laws of the United States, this Court must apply the precedents of the United States Court of Appeals for the Federal Circuit, which has jurisdiction over any appeal of this judgment. See 28 U.S.C. § 1295(a).

III. Analysis

A. Patent Infringement

One is liable for patent infringement if he or she,"without authority makes, uses, offers to sell, or sells any patented invention . . . during the term of the patent therefor . . . ." 35 U.S.C. § 271(a). Additionally, the filing of an application with the FDA under 21 U.S.C. § 355(j) "for a drug claimed in a patent" is an act of infringement "if the purpose of such submission"–as demonstrated in the applicant's paragraph IV certification–"is to obtain approval . . . to engage in the

commercial manufacture, use, or sale of [that] drug . . . before the expiration of such patent." 35 U.S.C. § 271(e)(2)(A).

Defendants concede infringing the claims of the '663 patent with their proposed ANDA products. SF 47. Thus, the only issues before the Court are those raised in Defendants' affirmative defenses to infringement: (1) whether the '663 patent is invalid due to obviousness, as asserted by Mylan and DRL, and (2) whether the '663 patent is unenforceable due to inequitable conduct, as asserted only by Mylan.

"A patent shall be presumed valid." 35 U.S.C. § 282. The validity of each claim within a patent must be evaluated independently; the invalidity of one claim does not disturb the presumption of validity of another. Id. The party challenging the patent bears the burden of proving by clear and convincing evidence the invalidity or unenforceability of the claims of a patent. Id. "The 'clear and convincing' standard of proof of facts is an intermediate standard which lies somewhere between 'beyond a reasonable doubt' and a 'preponderance of the evidence'" and "has been described as evidence which produces in the mind of the trier of fact an abiding conviction that the truth of [the] factual contentions [is] 'highly probable.'" Buildex, Inc. v. Kason Indus., Inc., 849 F.2d 1461, 1463 (Fed. Cir. 1988) (internal quotation omitted).

B. Obviousness

"[A] claimed invention is unpatentable if the differences between it and the prior art are 'such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art.'" Alza Corp. v. Mylan Labs., Inc., ___ F.3d ___, No. 06-1019, 2006 U.S. App. LEXIS 22616, at *4 (Fed. Cir. Sept. 6, 2006) (quoting 35 U.S.C. § 103(a)). Obviousness is a question of law. Id. at *4-5. Its resolution depends on four underlying factual inquiries, the so-called Graham[5] factors: "'(1) the scope and content of the prior art; (2) the level of ordinary skill in the prior art; (3) the differences between the claimed invention and the prior art; and (4) objective evidence of nonobviousness.'" Id. at *5 (quoting In re Dembiczak, 175 F.3d 994, 998 (Fed. Cir. 1999)).

1. The Scope and Content of the Prior Art

The scope and content of the prior art is limited to art that is analogous to the claimed invention. See In re Bigio, 381 F.3d 1320, 1325 (Fed. Cir. 2004). Analogous art is that which is from the same field of endeavor or, if not within the field of endeavor, is still reasonably pertinent to the particular problem with which the inventor is involved. Id.

[5] Graham v. John Deere Co., 383 U.S. 1 (1966).

The prior art includes (1) analogous patents or printed publications of a person besides the inventor in this or a foreign country before March 27, 1985, (2) analogous patents and printed publications of the inventor in this or a foreign country before March 27, 1984, and (3) analogous U.S. Patents (not invented by Kennis and Vandenberk) that issued after March 27, 1985 but were filed before – or were entitled to rely on a U.S. filing date before – March 27, 1985. 35 U.S.C. § 102(a), (b), and (e).

Defendants argue that the '663 patent is obvious in light of the drug pirenperone, which is covered by U.S. Patent No. 4,342,870 ("the '870 patent"). Pirenperone was also invented in part by Kennis. The '870 patent was assigned to Janssen, and issued more than one year prior to the filing date of the '663 patent. Thus, it is statutory prior art under 35 U.S.C. § 102(b).

Other patents and publications fall within the scope and content of the prior art, and will be discussed in more detail as necessary below.

2. The Level of Ordinary Skill in the Prior Art

The second Graham factor is the level of ordinary skill in the prior art. The obviousness analysis is conducted from the perspective of a person at that skill level. 35 U.S.C. § 103(a). This hypothetical person of ordinary skill is an objective legal construct who is presumed to be aware of all the relevant prior art.

Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc., 807 F.2d 955, 962 (Fed. Cir. 1986).

While the person having ordinary skill knows all of the prior art, he or she is neither a genius nor an innovator. "A person of ordinary skill in the art is also presumed to be one who thinks along the line of conventional wisdom in the art and is not one who undertakes to innovate, whether by patient, and often expensive, systematic research or by extraordinary insights, it makes no difference which." Standard Oil Co. v. Am. Cyanamid Co., 774 F.2d 448, 454 (Fed. Cir. 1985); see also Life Techs., Inc. v. Clontech Labs., Inc., 224 F.3d 1320, 1326 (Fed. Cir. 2000).

The parties in this case dispute the appropriate educational background of the person having ordinary skill in the art. Janssen argues such a person would have a master's degree in chemistry, medicinal chemistry, or pharmacy, or a bachelor's degree in one of those fields "with at least two years of experience in research in antipsychotic drugs." Pl.'s FF&CL, at p.24. Mylan and DRL claim that the person of ordinary skill would have a "Ph.D with at least two years of experience and a record of research success, which is attested to by a small group of publications." Defs.' FF&CL, at p. 49. The dispute appears to be somewhat

academic (so to speak).[6] Neither party contends that the educational background of the person of ordinary skill is determinative of whether the '663 patent is obvious or nonobvious. See, e.g., Meltzer Tr. 266:2-9, 19-24 (testifying that a person of ordinary skill with either educational background would find the '663 patent nonobvious); Wolff Tr. 530:19-25 (testifying that the person of ordinary skill would have possessed a doctorate, without stating that this educational level was essential to viewing the '663 patent as obvious). Additionally, neither party provided evidence on how specific items of prior art in the record would have been viewed differently depending upon the educational background of the person of ordinary skill.

Furthermore, it appears that few courts conducting an obviousness analysis ever specify the exact level of ordinary skill in the art. In the opinion of one authority, this is because, "[i]n practice, the concept of 'a person of ordinary skill in the art' seems more designed to remind judges to put themselves in the shoes of a skilled artisan, rather than to compel a specific factual finding." Roger Schechter & John Thomas, Principles of Patent Law, § 5.3.2.2 (2d ed. 2004). This view of the third Graham factor has some support in Federal Circuit case law. In

[6] The Court assures the reader that this is the only pun to be found in this lengthy opinion.

Environmental Designs, Ltd. v. Union Oil Co., 713 F.2d 693, 697 (Fed. Cir. 1983), the Court of Appeals explained that when evaluating the level of ordinary skill in the prior art,

> [t]he important consideration lies in the need to adhere to the statute, *i.e.*, to hold that an invention would or would not have been obvious, as a whole, when it was made, to a person of 'ordinary skill in the art' – not to the judge, or to a layman, or to those skilled in remote arts, or to geniuses in the art at hand.

With that said, the Federal Circuit has specified several factors to look at in defining the level of ordinary skill in the art. These factors that show that educational background is only part of the story. See Orthopedic Equipment Co. v. All Orthopedic Appliances, Inc., 707 F.2d 1376, 1382 (Fed Cir. 1983). They include: "(1) the educational level of the inventor; (2) types of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field." Environmental Designs, 713 F.2d at 696 (citing Orthopedic, 707 F.2d at 1382).

Here, the '663 patent's inventor, Kennis, has a degree in industrial engineering from a foreign university that he testified was not capable of comparison to a Bachelor of Science or a Bachelor of Arts. Kennis Dep. (10/20/2004) Tr. 11:19-13:8. In any event, Kennis stated that he is not a doctor.

Id. at 11:17-18. Additionally, Dr. Meltzer testified that the actual workers involved in the development of antipsychotic compounds have bachelor's or master's degrees, not doctorate degrees. Meltzer Tr. 266:15-18; see also Strupczewski Dep. (11/16/2004) Tr. 13:15-23. The Court finds this testimony persuasive, and finds that the person of ordinary skill in the art in 1985 searching for an antipsychotic compound with reduced EPS would have had a master's degree in chemistry, medicinal chemistry, or pharmacy, or a bachelor's degree in one of those fields with at least two years of experience in research in antipsychotic drugs.[7]

To the extent the parties presented evidence bearing on the remaining factors articulated in Environmental Designs, 713 F.2d at 696, they are considered in the analysis below in determining whether the person of ordinary skill in 1985 would have found the '663 patent obvious.

3. The Differences Between the Claimed Invention and the Prior Art

[7] The Court stresses however, that its ultimate ruling–that the '663 patent is nonobvious and therefore not invalid–is not contingent upon this finding. Indeed, the Court would find the '663 patent nonobvious even were it to hold that the person of ordinary skill in the art possessed a doctorate degree. As stated above, the parties have not presented any evidence that particular pieces of prior art would have been viewed any differently if the person evaluating it had a bachelor's, master's or doctorate.

"For a chemical compound, a prima facie case of obviousness requires 'structural similarity between claimed and prior art subject matter . . . *where the prior art gives reason or motivation to make the claimed compositions*.'" Yamanouchi Pharm. Co. v. Merck & Co., 231 F.3d 1339, 1343 (Fed. Cir. 2000) (emphasis added) (quoting In re Dillon, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc)).

Because 35 U.S.C. § 103(a) orders a Court to determine whether the subject matter was obvious "at the time the invention was made," the obviousness inquiry cannot be performed using hindsight. Accordingly, this Court must apply the "motivation-suggestion-teaching" test, which asks "whether a person of ordinary skill in the art, possessed with the understandings and knowledge reflected in the prior art, and motivated by the general problem facing the inventor, would have been led to make the combination recited in the claims." In re Kahn, 441 F.3d 977, 988 (Fed. Cir. 2006) (citing Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc., 424 F.3d 1293, 1321-24 (Fed Cir. 2005)).

It is not enough for a party seeking to defeat a patent on obviousness grounds to merely identify each element of the invention in the prior art. Id. at 986. This can be done for nearly all inventions. Id. Instead, a prima facie case of obviousness requires the party to "explain the reasons one of ordinary skill in the

art would have been motivated to select the references and to combine them to render the claimed invention obvious." Id. (internal quotations omitted).

Evidence of a "motivation to combine" need not be found explicitly in the prior art–it "may be implicit from the prior art as a whole." In re Kotzab, 217 F.3d 1365, 1370 (Fed. Cir. 2000). If such evidence is lacking, however, the use of hindsight will be inferred. Kahn, 441 F.3d at 986.

a. Defendants' Obviousness Argument

Mylan and DRL do not argue that risperidone would have been obvious; instead they claim that *compound 11* would have been obvious in 1985 in light of the prior art. As mentioned earlier, risperidone and compound 11 are embodiments of all 18 claims in the '663 patent. SF 17. The claims are written in the Markush format. "A Markush group is a listing of specified alternatives of a group in a patent claim." Abbott Labs. v. Baxter Pharm. Prods., 334 F.3d 1274, 1280 (Fed. Cir. 2003). "[M]embers of the Markush group are . . . alternatively usable for the purposes of the invention." Id. (internal quotations omitted). Because the '663 patent's claims are written this way, Janssen "has made a representation that for the purposes of the claimed invention, the [embodiments] of the group[s] are equivalents." In re Skoll, 523 F.2d 1392, 1397 (CCPA 1975). As a result, if one embodiment of a group is obvious, e.g., compound 11, Janssen is

precluded from arguing that any other embodiment of the claim, e.g., risperidone, is not obvious. Id.; see also Ecolochem Inc. v. So. Cal. Edison Co., No. 95-1320, 1996 U.S. App. LEXIS 13330, at *6 (Fed. Cir. June 5, 1996) (not published) ("By claiming a Markush group, [the patentee] has indicated that for the purpose of claim validity, the members of the claimed group are functionally equivalent. Thus if utilizing one element of the group is anticipated or obvious, the patentee is precluded from arguing that the claim is valid.").

Pirenperone, of the '870 patent, is structurally identical to compound 11 with one exception: pirenperone has a ketone group, where compound 11 has a benzisoxazole group. Wolff Tr. 547:8-548:24. Mylan and DRL argue that a person of ordinary skill in the art in 1985 would have been motivated from the prior art to start with pirenperone, and take the following series of allegedly obvious steps in order to arrive at compound 11.

First, Defendants claim that pirenperone would have been chosen as a lead compound by one looking for an antipsychotic with minimal side effects, including EPS, because it possessed indicators of those properties. Second, Defendants claim that once pirenperone was chosen, it would have been obvious to the person of ordinary skill in 1985 that its only problem was that it had a short half-life, and thus had to be administered to patients three times per day, which

was a problem for schizophrenics. Third, given the prior art, Mylan and DRL believe it then would have been obvious that pirenperone's ketone group was responsible for this durational problem. Fourth, it then would have been obvious, Defendants assert, to the person of ordinary skill that the solution to this problem was to convert the ketone group to a benzisoxazole, and that this change would permit the compound to retain its desired antipsychotic activity with low side effects.

The Court concludes that Mylan and DRL have failed to prove by clear and convincing evidence that all of these steps would have been obvious to the person of ordinary skill in the art in 1985. Indeed, they have failed to prove that *any* would have been obvious.

b. <u>The Person of Ordinary Skill Would Not Have Chosen Pirenperone as a Lead Compound</u>

Defendants argue that the person of ordinary skill in the art in 1985 would have started with pirenperone in attempting to create an antipsychotic with reduced EPS, because pirenperone possessed properties that the prior art taught would be needed for such a drug, namely, dopamine antagonism and serotonin antagonism.[8]

[8] A short biochemistry lesson, provided by the parties, is in order.

(continued...)

As stated earlier, when applying the "motivation-suggestion-teaching" test, the Court must ask whether the person of ordinary skill in the art in 1985, "motivated by the general problem facing the inventor would have been led to make the combination recited in the claims." Kahn, 441 F.3d at 988 (internal quotations omitted). The "general problem" in 1985 was how to develop a safe and effective antipsychotic with reduced EPS. McMillen Tr. 483:11-484:18; Wolff Tr. 618:5-8. Therefore, Mylan and DRL must demonstrate why the

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[8](...continued)
Dopamine and serotonin are hormones that, when found in the brain, act as neurotransmitters. A neurotransmitter is a chemical that permits the billions of nerve endings in the brain to communicate with each other. In turn, this communication enables a human being to function.

Each nerve ending in the brain contains dozens of different "receptors." Neurotransmitters attach to the receptors and cause a chemical reaction. However, in the same way that only certain keys will open certain locks, only certain neurotransmitters will attach to certain receptors. For example, there are receptors that will only allow dopamine (and similar chemicals) to attach, and receptors that will only allow serotonin to attach. Receptors are categorized by what neurotransmitter can attach to it, and within these categories, there are further subcategories. For example, there are five types of dopamine receptors.

Pharmaceutical companies can create drugs that mimic the actions of neurotransmitters. These drugs attach to receptors and behave like a particular neurotransmitter. Such drugs are called "agonists." For example, a drug that mimics the functioning of dopamine is called a "dopamine agonist."

Conversely, drugs can be created that block the actions of neurotransmitters. These drugs attach to particular receptors and prevent neurotransmitters from attaching. Such drugs are called "antagonists." For example, a drug that blocks the functioning of dopamine is called a "dopamine antagonist." Meltzer Tr. 227:20-232:24; Pl.'s FF&CL, at app. A.

hypothetical person would have been motivated to choose pirenperone as a lead compound in attacking this general problem.[9] See Yamanouchi, 231 F.3d at 1344. First, Defendants argue that tests in the prior art demonstrate that pirenperone was a dopamine antagonist, and therefore the prior art teaches that pirenperone would be an effective antipsychotic. Second, Defendants claim that pirenperone would have been thought to have a low incidence of EPS due to its serotonin antagonism.

The Court concludes that Defendants are incorrect on both points. First, the prior art teaches that in 1985 pirenperone was an antianxiety drug, not an

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[9] Mylan and DRL dispute that Yamanouchi "'mandates' the identification of a lead compound as a predicate to an obviousness analysis," and suggest that they need not demonstrate why one of ordinary skill in the art in 1985 would start with pirenperone. Defs.' Findings of Fact and Conclusions of Law ("FF&CL") 61-62. The Court disagrees. The Federal Circuit's statement in Yamanouchi that "[a]t the outset, [the Defendant] did not show the required motivation for selecting example 44 as a lead compound," 231 F.3d at 1345, was not the creation of a new legal requirement, but merely a factually-specific application of the "motivation-suggestion-teaching" test. As explained earlier, in cases involving chemical compounds, the party alleging the obviousness of the patent must demonstrate that "'the prior art gives reason or motivation to make the claimed compositions.'" Id. at 1343 (quoting In re Dillon, 919 F.2d at 692). The Yamanouchi Court faulted the Defendant there for failing to show motivation for selecting example 44 as a lead compound because *it was the Defendant's own allegation* that "one of skill in the art would have considered it obvious to select the example 44 compound from [a prior art patent] and [a compound from another prior art patent] to use as leads for making [a compound in the disputed patent]." Id. at 1343-44. Similarly here, it is *Mylan and DRL* which allege that one of ordinary skill in the art in 1985 would have started with pirenperone, see, e.g., Defs.' FF&CL, p. 34; Defs. Post-Trial Br. 6-7, and that is precisely why this Court is requiring Defendants to prove that the prior art teaches the motivation to do so. See In re Dillon, 919 F.2d at 692.

antipsychotic. Second, one following the conventional wisdom in 1985 for choosing a drug with reduced EPS would not have selected pirenperone because that wisdom did not emphasize serotonin antagonism. The prior art provided other more likely starting points for the development of an improved atypical antipsychotic drug.

(1) Pirenperone Was Not Considered an Antipsychotic

Pirenperone's failure of standard tests for antipsychotics indicates that it would not have been considered an antipsychotic and thus, would have made an unlikely choice as a starting point. Meltzer Tr. 274:3-275:5; PX 94; PX 388; PX 389.

As both of Defendants' experts admitted, no prior art described pirenperone as an antipsychotic. No prior art said that pirenperone was being considered or should be considered as an antipsychotic drug. No prior art tested pirenperone as an antipsychotic in humans. Wolff Tr. 638:23-639:5, 641:6-8, 641:18-20; McMillen Tr. 511:8-10. Instead, pirenperone was recognized in the literature to be a pure serotonin antagonist that might be clinically useful to treat anxiety. Meltzer Tr. 269:5-8; PX 22; PX 94; PX 96; PX 202; PX 388; PX 389.

Janssen—the company that invented pirenperone and knew it best—did not

view pirenperone as a potential antipsychotic drug. Meltzer Tr. 271:18-22. Indeed, the pirenperone patent does not even mention that pirenperone might be an antipsychotic. PX 80; Wolff Tr. 641:3-5; Meltzer Tr. 269:15-20. Instead, that patent describes the pirenperone family of compounds as "very potent serotonin[] antagonists" to "be used in the treatment of a variety of diseases in which serotonin release is of predominant importance." PX 80, col. 11, ll. 11-14; Wolff Tr. 639:15-22. The patent focused on pirenperone's serotonin antagonist qualities with no indication of antipsychotic potential. Meltzer Tr. 269:12-25; Wolff Tr. 639:6-14; PX 80 (abstract). On the basis of this evidence, the Court concludes that Janssen did not view pirenperone as a potential antipsychotic.

In addition, the published literature consistently describes pirenperone as a pure serotonin antagonist that could be useful to treat anxiety disorder. Janssen conducted extensive research on pirenperone. In both its published and unpublished research, Janssen studied and described pirenperone only as a treatment for anxiety. Wolff Tr. 638:1-10, 641:9-17; Meltzer Tr. 270:1-8; McMillen Tr. 508:21-509:4. Janssen's studies make this clear. See PX 21, 22, 93, 96, 202.

As Defendants' expert witness Dr. Brian McMillen testified, antianxiety drugs can sometimes be used for antipsychotic purposes, "depend[ing] on the dose

and activity" of the drug. McMillen Tr. 470:25-471:5. It is apparent, however, that the two classes of drugs are not interchangeable. The testimony of Dr. Herbert Meltzer, and the prior art, demonstrated that an antianxiety drug will not always successfully function as an antipsychotic. Meltzer Tr. 272:1-19; PX 94, PX 388, PX 389.

Indeed, prior art was explicit that pirenperone failed to function as an antipsychotic. In three published studies on pirenperone and another of its compounds, setoperone, Janssen told the world that setoperone was an antipsychotic, while pirenperone was not. PX 94; PX 388; PX 389; McMillen Tr. 509:16-510:11; Meltzer Tr. 272:1-272:19, 273:12-275:5.

Mylan and DRL rely solely on the fact that pirenperone, in addition to its serotonin antagonism, is a dopamine antagonist to support their claim that pirenperone is an antipsychotic. See, e.g., Defs.' FF&CL, p. 35; McMillen Tr. 479:15-20; Meltzer Tr. 275:6-11. Not all dopamine antagonists are effective antipsychotics, however. Meltzer Tr. 275:25-276:17. Therefore, companies such as Janssen developed, used, and published tests, in addition to those for dopamine antagonism, to determine whether a compound would be an antipsychotic. Meltzer Tr. 271:18-272:19. While setoperone passed these additional tests, pirenperone failed them. Meltzer Tr. 271:18-272:19, 273:12-275:5; McMillen Tr.

509:16-510:11; PX 94; PX 388; PX 389.

For example, Dr. Janssen tested both setoperone and pirenperone twice using food reinforcement, cocaine discrimination and fentanyl discrimination. Passing the food reinforcement tests as evidenced by suppression of response control is an effect that is characteristic of antipsychotic activity. The published results demonstrated that setoperone passed both tests. By contrast, pirenperone failed the same standard tests for antipsychotic activity. Wolff Tr. 643:9-15; Meltzer Tr. 273:12-274:12; PX 94; PX 388; PX 389. Thus, setoperone was unique in combining LSD antagonism (i.e., serotonin antagonism, an effect shared with pirenperone) with typical antipsychotic activity. Wolff Tr. 642:22-25; PX 94. As a result of these studies, Janssen studied setoperone, not pirenperone, in humans to treat schizophrenia. PX 391; PX 392; Wolff Tr. 634:12-635:7. It is clear from these test results that a person of ordinary skill would have not considered pirenperone an antipsychotic.

The same studies also tested pirenperone for antianxiety activity. In those tests, unlike the antipsychotic tests, pirenperone performed better than setoperone. Dr. Janssen reported that pirenperone was effective in the antianxiety tests and had the potential to be another Librium or Valium—known antianxiety drugs. PX 94; Meltzer Tr. 274:13-23. As a result, Janssen studied pirenperone only as a

treatment for anxiety in humans.

Dr. Janssen's three publications told one of ordinary skill in the art that pirenperone is an anxiety drug and that it is not an antipsychotic. A person of ordinary skill in the art in 1985, trying to develop an antipsychotic drug, would not turn to pirenperone in light of that prior art. Meltzer Tr. 275:2-5.

Even Dr. Manfred Wolff, Mylan and DRL's expert witness on obviousness, agreed that one of ordinary skill in the art would hesitate go against Dr. Janssen's recommendation on pirenperone:

> Q. Now, we are talking about the person of ordinary skill and about a compound. Pirenperone is patented as a pure serotonin antagonist, is being studied only in anxiety and Dr. Janssen who you think the ordinary scientist would give so much deference, is telling the world pirenperone is not an antipsychotic, *you think a person of ordinary skill would go against Dr. Janssen's recommendation?*
> A. *Perhaps not.*

Wolff Tr. 643:20-644:2 (emphasis added).

Dr. Wolff's "perhaps not" makes it clear that Mylan and DRL have failed to prove by clear and convincing evidence that it would have been obvious for one of ordinary skill in the art in 1985 to select pirenperone as a starting point to develop an antipsychotic drug.

(2) <u>The Conventional Wisdom in 1985 for Predicting Whether a Drug Would Have</u>

Reduced EPS Teaches Away From Selecting Pirenperone as a Lead Compound

There is a second flaw in Mylan and DRL's argument that pirenperone would have been chosen as a lead compound. They assert that it was well known in 1985 that all that was needed to create an antipsychotic drug with reduced EPS was to find a compound, like pirenperone, with combined serotonin and dopamine antagonism. See, e.g., Defs.' FF&CL, pp. 35-37. This, however, was not the conventional wisdom in 1985.

To the contrary, nearly all the prior art typical antipsychotic drugs–drugs that caused debilitating EPS–were also combined serotonin-dopamine antagonists. Meltzer Tr. 247:2-14, 260:23-261:2; PX 98, p. 170 at Table 2. It was only first demonstrated by Dr. Meltzer much later, in 1989, that a particular ratio of serotonin and dopamine antagonism is critical to creating an atypical antipsychotic. PX 14; Meltzer Tr. 247:20-24. As it happens, the compounds of the '663 patent, risperidone and compound 11, both have the desirable dopamine-serotonin ratio, and that is part of the reason for their effectiveness. PX 1. But simply being a serotonin-dopamine antagonist, like pirenperone, is not enough and knowledge of the desirable ratio comes from pure hindsight; it is not recited anywhere in the prior art.

In the early 1980s, numerous theories were put forward regarding the role of

the brain's receptors in schizophrenia and how to reduce EPS. Meltzer Tr. 237:15-238:11, 242:13-243:1; McMillen Tr. 503:23-504:9.

The prior art demonstrated that the dominant theory in March 1985 was the anticholinergic theory, which focused not on serotonin, but on acetylcholine–another of the brain's many neurotransmitters. It was believed that the combination of antidopamine and anticholinergic[10] (acetylcholine-blocking) activities would lead to an atypical antipsychotic with reduced EPS. Meltzer Tr. 262:8-10; 248:3-11.

This theory was developed by comparing the anticholinergic activity of known drugs. Researchers such as Dr. Solomon Snyder found that clozapine, which had the lowest level of EPS, was the strongest anticholinergic. Meltzer Tr. 238:2-14, 240:11-241:14; Wolff Tr. 627:23-628:1; PX 265. By contrast, haloperidol, a typical antipsychotic that produced the most EPS, was the weakest anticholinergic. Meltzer Tr. 241:19-21; Wolff Tr. 628:2-6.

As Dr. Snyder put it:

> There was an inverse correlation between EPS incidence and anticholinergic potency, with clozapine being the most potent anticholinergic and butyrophenone

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[10] The term anticholinergic is sometimes also referred to as antimuscarinic, Meltzer Tr. 240:20-21, because a subclass of acetylcholine receptors are also sensitive to the neurotransmitter muscarine. Pl.'s FF&CL, at app. A.

> haloperidol the weakest, findings obtained independently by Miller and Hiley (Table 2).

PX 36 at 988.[11] See also Wolff Tr. 628:7-17.

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[11] Indeed, the prior art in evidence is replete with teachings that the anticholinergic theory was the conventional wisdom in the 1970s, 1980s and beyond: Snyder wrote in 1974 that "[t]he *most potent anticholinergics* should evoke the fewest extrapyramidal effects; conversely, drugs with the highest incidence of these side effects should be the weakest anticholinergics." PX 265 at 1248 (emphasis added).

Miller and Hiley concluded in 1974 that "[t]he results obtained here support the hypothesis that the *antimuscarinic activity* of these drugs is related to the frequency of extrapyramidal side effects." PX 725 at 596 (emphasis added).

Creese said in 1976: "The *anticholinergic properties* of these drugs may well account for their low incidence of extrapyramidal effects." PX 178 at 482 (emphasis added).

Neumeyer – one of Defendants' experts – reported in 1981: "The *most potent anticholinergics* should evoke the fewest extrapyramidal effects; conversely, drugs with the highest incidence of these side effects should be the weakest anticholinergics." PX 728 at 215 (emphasis added).

Chakrabarti – an Eli Lilly researcher – reported in 1982: "In fact, neuroleptics, which possess anticholinergic properties (clozapine, thioridazine), produce a reduced incidence of EPS in the clinic. . . . Thus, in order to achieve a maximum reduction in side effects, it is important to obtain a correct balance of the antidopaminergic and *anticholinergic activities*." PX 753 at 1133 (emphasis added).

The anticholinergic theory continued to be important well after 1985. For example, Neumeyer continued to emphasize it in 1989 and 1995 texts: "With the phenothiazines and butyrophenones, and virtually all other classes of antipsychotic drugs, extrapyramidal side effects vary directly with the ratio of their anti-D-2; *anti-Achn [anti-acetylcholine] potency*." PX 754 (1989) at 198 (emphasis added); PX 274 (1995) at 208; Wolff Tr. 629:21-630:1.

The anticholinergic theory was used by scientists such as Strupczewski and his co-workers at Hoechst-Roussel (Aventis) as well as Eli Lilly and Sandoz. Hoechst-Roussel based its drug design program in the 1980s on the

(continued...)

The theory had strong intuitive appeal. For many years the medical community had used anticholinergic drugs to treat EPS. Patients were given antipsychotic drugs that were dopamine antagonists together with an anticholinergic drug to treat their EPS side effects. Meltzer Tr. 235:18-236:1.

Mylan and DRL were unable to effectively rebut Dr. Meltzer's testimony and the prior art in the record, which demonstrated that the anticholinergic theory was the conventional wisdom in 1985 for producing a compound with reduced EPS. See Wolff Tr. 631:4-10; McMillen Tr. 503:23-504:9. Neither Dr. Wolff nor Dr. McMillen was able to disagree with Dr. Meltzer's assessment that the anticholinergic theory was dominant and that the serotonin theory, which Defendants now claim the person of ordinary skill would have followed, was controversial. Id.

Pirenperone has no anticholinergic activity. Meltzer Tr. 242:10-12, 248:9-13, 267:10-11. Indeed, the anticholinergic theory discounted the relevance of serotonin. Meltzer Tr. 245:5-8; PX 36 at 988.

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[11](...continued)
anticholinergic theory. As part of this program, Hoechst-Roussel developed compounds disclosed in its U.S. Patent No. 4,352,811 ("the '811 patent"), PX 81, and in the 1982 Strupczewski Abstract, PX 191. Strupczewski Dep. (11/16/2004) Tr. 151:14-152:15, 105:12-23. Eli Lilly and Sandoz followed the anticholinergic theory by working with its premiere example – clozapine. Meltzer Tr. 249:22-250:17.

There were numerous other theories in 1985 in addition to the dominant anticholinergic theory. These included: (1) dopamine 1 (D1) receptor, (2) norepinephrine, (3) GABA, and (4) glutamate. The D1 receptor and chemicals in the brain (norepinephrine, GABA, glutamate) were viewed as potentially causative of schizophrenia and researchers tried to find drugs that would antagonize them in order to treat it. Meltzer Tr. 242:13-243:1; McMillen Tr. 504:4-6.

Defendants point to a few papers that suggested that serotonin may play some role in schizophrenia. In particular, Defendants rely on a 1978 study by Dr. Josee Leysen (a Janssen scientist) in support of the idea that serotonin antagonism was important to develop an antipsychotic with reduced EPS and that a dopamine-serotonin theory would be followed by one of ordinary skill in the art in 1985. PX 98. But as Dr. Wolff conceded, there is no basis for that idea in the Leysen article. Nowhere does Leysen say anything about EPS or whether serotonin is good, bad, or indifferent for EPS. Wolff Tr. 632:6-9.

As reported in that article, Dr. Leysen simply analyzed a large number of antipsychotics. PX 98 at Table 2; Wolff Tr. 631:18-20. She determined that many antipsychotic drugs had antiserotonin properties, but concluded that "[t]he precise significance of the anti-serotonergic component of neuroleptics, however, requires assessment of its clinical implications." PX 98 at 171; Wolff Tr. 632:1-5; 634:2-6.

As this passage makes clear, Dr. Leysen had no understanding of the clinical relevance of serotonin. Meltzer Tr. 245:12-19.

Defendants also point to a few papers that postulate that antiserotonin properties might contribute to the reduction of EPS and invite further investigation. But even the proponents of serotonin recognized the anticholinergic theory as attractive. Wolff Tr. 626:11-13. At best, these isolated papers invite further experimentation so that the effects of serotonin could also be considered.[12]

None of the developing theories on serotonin dislodged the anticholinergic theory as the dominant theory in 1985. Meltzer Tr. 246:24-247:1.

Unlike the anticholinergic theory, the serotonin theory had significant limitations. While the serotonin theory postulated that serotonin antagonism

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[12] For example, Anthony Sulpizio, et al., PX 38, wrote that clozapine's antiserotonin properties might contribute to its overall pharmacological profile, but he did not discount the need for anticholinergic properties. Meltzer Tr. 246:5:-18. Rather, Sulpizio called the anti-cholinergic theory "important": "[S]ome authors have suggested that clozapine's potent muscarinic blocking activity explains its lack of EPS liability.… [I]nvestigations into the anti-dopamine and anti-cholinergic activity of clozapine are obviously important in elucidating its overall pharmacological profile, our data suggest that the study of clozapine's anti-serotonin activity is of equal importance." PX 38 at 1445.

Similarly, Dr. Lai, PX 37, wrote that "[w]hile the intrinsic anticholinergic activity hypothesis offers an attractive explanation for the lower EPS of thioridazine and clozapine, the possible role of serotonergic mechanism in this phenomenon is also worthy of consideration." PX 37 at 347; Wolff Tr. 626:6-10.

would reduce EPS, typical antipsychotics caused EPS despite their potent serotonin antagonism. There was no explanation for these observations. For example, chlorpromazine, a typical antipsychotic with a high incidence of EPS, had strong serotonin antagonism. Meltzer Tr. 247:2-14, 260:23-261:2; PX 98, p. 170 at Table 2.

As a result, there was skepticism in the pharmaceutical industry about the value of serotonin antagonism. For example, from 1982 to 1986 Bristol-Myers and Defendants' expert Dr. McMillen were developing a serotonin agonist, not antagonist. McMillen Tr. 502:15-21, 504:12-19, 505:1-19, 506:20-23. Additionally, Hoechst-Roussel did not even investigate the serotonin activity of the benzisoxazole compounds from the Strupczewski patent, PX 81, that Defendants rely on. Strupczewski Dep. (11/16/2004) Tr. 113:23-114:6, 115:9-20, 116:7-19.

The prior art demonstrates that the serotonin theory was just one of numerous theories, and that it was considered controversial. The articles cited by Mylan and DRL invite further investigation into the role of serotonin in reducing EPS; however, this is not a sufficient reason to select pirenperone–a serotonin antagonist with no anticholinergic activity–as a lead compound. "The prior art must be considered as a whole for what it teaches." Medichem, S.A. v. Rolabo,

S.L., 437 F.3d 1157, 1166 (Fed. Cir. 2006).

Further, even if the serotonin theory were selected, that was no reason to pick pirenperone among the many possible dopamine-serotonin antagonists. Rather, as noted above, pirenperone would not be selected since it was known neither as an antipsychotic nor as an agent that reduced EPS.

Instead, a person of ordinary skill in the art in 1985 would follow the "conventional wisdom in the art," Standard Oil, 774 F.2d at 454, and use the anticholinergic theory in order to develop an improved antipsychotic with reduced EPS. Meltzer Tr. 267:4-14. That person of ordinary skill in the art following the dominant anticholinergic theory would select compounds such as clozapine or thioridazine to develop an antipsychotic drug with reduced EPS. These drugs were known antipsychotics with potent anticholinergic properties. Meltzer Tr. 249:22-250:2. On the other hand, pirenperone would never be selected. Unlike clozapine, pirenperone is not an anticholinergic. Meltzer Tr. 242:10-12, 248:3-13, 267:10-11.

(3) Defendants Admit Using Hindsight to Choose Pirenperone

To avoid using hindsight, a proper obviousness analysis asks whether a person having ordinary skill in the art when "confronted with the same problems

as the inventor *and with no knowledge of the claimed invention*, would select the elements from the cited prior art references for combination in the manner claimed." In re Rouffet, 149 F.3d 1350, 1357 (Fed. Cir. 1998) (emphasis added).

Almost any invention, no matter how nonobvious at the time, will appear obvious when looking backward from the solution. It is for that reason that "[c]are must be taken to avoid hindsight reconstruction *by using 'the patent in suit as a guide through the maze of prior art references*, combining the right references in the right way so as to achieve the result of the claims in suit.'" Grain Processing Corp. v. Am. Maize-Prods. Co., 840 F.2d 902, 907 (Fed. Cir. 1988) (citation omitted, emphasis added).

Mylan and DRL's experts admit that they went straight to pirenperone solely to advance their theory of obviousness, not because a person of ordinary skill in the art would choose pirenperone. McMillen Tr. 508:12-20; Wolff Tr. 621:14-622:11, 637:9-11. Dr. McMillen did not consider the known antipsychotics in the prior art and did not purport to offer an opinion as to why a person of ordinary skill in the art would have focused on pirenperone. Instead, he focused on pirenperone alone because it was close to the claims in the '663 patent. McMillen Tr. 501:12-502:3, 508:12-20 ("Q. And one of the reasons that you didn't go and consider setoperone was that pirenperone was closer to all of the

claims in the '663 patent and setoperone wasn't as close to all of the claims in the '663 patent. Correct? A. Correct.").

Dr. Wolff, Defendants' only expert to offer an obviousness opinion, was no different. He admitted he did nothing to learn about antipsychotic drug research in the early 1980s. Wolff Tr. 603:18-604:20. This is despite the fact that the prior art includes thousands of actual antipsychotic compounds, falling into numerous broad classes. Meltzer Tr. 249:7-21; PX 16. Dr. Wolff also said he did not know what drugs researchers were looking for to reduce EPS. Wolff Tr. 605:20-606:24. Instead, he testified that his analysis began and ended with pirenperone "because of its relationship to the claims of the patent." Wolff Tr. 614:17-21, 612:10-13, 637:9-11 On cross examination, Dr. Wolff was asked:

> Q. To summarize your approach so far in reaching your conclusion [on selecting a lead compound for your obviousness analysis], you looked at the structure of compound 11, you looked at the structure of the compound pirenperone, and you did the structural analysis.
> A. That's correct.

Wolff Tr. 548:20-24.

This use of the '663 patent as a guide was improper because one of ordinary skill in the art in 1985 would not have the benefit of starting from the '663 patent, in order to choose pirenperone. See Yamanouchi, 231 F.3d at 1345.

Mylan and DRL's failure to prove by clear and convincing evidence that the person of ordinary skill in the art in 1985 would have selected pirenperone in attempting to create a safe and effective atypical antipsychotic alone is sufficient to defeat their claims of obviousness. Nevertheless, the Court will describe below why Mylan and DRL have failed to demonstrate, even assuming choosing pirenperone would have been obvious, that it was obvious to modify it in such a way as to result in compound 11.

c. A Person of Ordinary Skill in the Art in 1985 Would Not Have Been Motivated to Modify Pirenperone's Ketone Group to Make it Long-Lasting

(1) It Would Not Have Been Obvious That Pirenperone Had a Short-Duration Problem

After choosing pirenperone, Mylan and DRL argue it would have been obvious to one of ordinary skill in the art in 1985 that it was short-lasting, requiring a patient to take it three times per day. This would have been an obvious problem for an antipsychotic drug, Defendants claim, because a patient with schizophrenia, suffering from its cognitive impairments, may not remember to take the drug that often. See Wolff Tr. 560:15-561:6.

Defendants rely on papers by Meltzer, DX 113, and Green, PX 25, to support their assertion that pirenperone was short-lasting. Green found that at low

doses, pirenperone's ability to affect a particular test result in a rat lasted less than six hours. From this, Green concluded that pirenperone was "fairly short-lasting." PX 25 at 577. The Meltzer paper, another rat study, looked at pirenperone's effects on hormonal secretion, and said nothing about pirenperone's duration at all. McMillen Tr. 511:14-23; PX 25; DX 113.

The first problem with these articles is that they provide rat data, not human data. Dr. McMillen agreed that "the duration of action of a[n antipsychotic drug] may be very different in rat and man[.]" McMillen Tr. 511:24-512:14; Meltzer Tr. 280:4-10. This is supported by prior art. DX 62 at 2213 ("It is known that the duration of action and oral absorption of neuroleptics may be very different in the rat and man.").

There are other issues associated with the articles that would cause one of ordinary skill not to focus on them. As for the Meltzer article, it does not describe pirenperone as having a short duration, even in rats. DX 113. The Green article does comment on pirenperone's duration, but the Court agrees with Dr. Meltzer's assessment that it would have been discounted by one of ordinary skill for a few reasons. Specifically, Green did not (1) show the data, (2) show the standard error, (3) report how many animals were studied, or (4) study time intervals between 60 minutes and six hours. Given these defects, there was not much to be

learned from Green – and the person of ordinary skill would not have relied on it to conclude that pirenperone was short acting in humans. Meltzer 278:17-279:1, 279:15-280:3; PX 25 at 575.

The second problem with Defendants' approach is that it looks at the rat data to the exclusion of any other references, such as the extremely relevant and important *human* test data.

In examining the prior art to see what it teaches a person of ordinary skill, references cannot be read in isolation. Instead, they must be read in light of what they fairly teach in combination with the prior art as a whole. Mylan and DRL cannot pick and choose among the prior art references. See, e.g., In re Merck & Co., 800 F.2d 1091, 1097 (Fed. Cir. 1986).

When all of the prior art available in March 1985 – and not just the rat data relied on by Defendants – is considered, it shows that pirenperone was acceptable for human use without modification. Janssen was going forward with clinical studies of pirenperone in humans using three times a day dosing. Wolff Tr. 646:14-21; PX 202; PX 96; PX 22. No suggestion was made in any of Janssen's studies with pirenperone in humans that its duration was inadequate. No suggestion was made that pirenperone should be modified in any way.

This is not surprising considering, first, the fact that a drug is dosed three

times a day in clinical trials does not indicate that it could not be dosed on a less frequent schedule after full testing, particularly in antianxiety drugs. Meltzer Tr. 281:9-20. Second, three times a day dosing has been shown to be perfectly acceptable for antipsychotic drugs. Testimony from the only two expert witnesses who are medical doctors that prescribe antipsychotics, stated that haloperidol, the leading antipsychotic drug at the time, was dosed three times a day. Meltzer Tr. 281:21-24; Tamminga Tr. 50:17-20, 72:17-19; see also Wolff Tr. 648:5-11.

Defendants' experts admitted they lacked the expertise to challenge this point. Wolff Tr. 647:16-23; McMillen Tr. 502:4-11. Dr. Wolff conceded that it was not a necessity, but only a choice, to change the dosing on a drug proven effective at three times a day. Wolff Tr. 649:17-20.

This is especially true given that compound modification is an uncertain process that can easily result in reduced efficacy or safety issues. Wolff Tr. 650:8-13, 651:4-8. By Dr. Wolff's own estimate, a compound modification results in a desirable change only five to 10 percent of the time. Wolff Tr. 651:16-24. With that level of risk and uncertainty and with three times a day dosing a medically acceptable alternative, Mylan and DRL failed to provide clear and convincing evidence that a person of ordinary skill would conclude that pirenperone had a short-duration problem that could only be solved by modifying its molecular

structure.

In sum, it would not have been obvious to the person of ordinary skill in the art in 1985 that pirenperone was short-lasting and that this was a problem requiring a modification of its molecular structure.

(2) Even if Pirenperone's Duration Was a Problem, It Would Not Have Been Obvious That Metabolism at its Ketone Group Was the Cause

As stated above, pirenperone is structurally identical to compound 11 except pirenperone has a ketone group where compound 11 has a benzisoxazole group. Wolff Tr. 547:8-548:24. Mylan and DRL claim that it would have been obvious to the person of ordinary skill in 1985 that pirenperone's short duration was due to metabolism[13] at this ketone group.

Again, the Court disagrees. Even were the Court to assume that pirenperone had a short-duration problem, and that modifying the compound was the solution, Mylan and DRL have failed to provide clear and convincing evidence that it

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[13] The term "metabolism" comprises the sum of the physical and chemical processes in an organism by which its material substance is produced, maintained, and destroyed, and by which energy is made available. See Pl.'s FF&CL, app. A.

The liver is responsible for metabolizing foreign substances that enter the body, like pharmaceuticals. The liver "[t]ries to get rid of drugs, anything foreign in the body that is not normally, should be there, the job of the liver is to either make it more soluble, cut it apart, get rid of it, make it nontoxic, if possible." Abraham Tr. 387:22-25. Certain drugs are metabolized, and others are not. Id. at 388:3-4.

would have been obvious that metabolism at the ketone was the problem.

It was not known in 1985 that pirenperone metabolized, let alone that it metabolized at the ketone. Abraham Tr. 386:5-10. Because there is no teaching in the prior art that pirenperone had a metabolism issue at the ketone, the person having ordinary skill who follows conventional wisdom would not assume the problem was at the ketone. See Standard Oil, 774 F.2d at 454.

If one concluded that pirenperone was short acting in humans, the problem could be due to any number of factors, such as absorption, distribution, metabolism, or excretion. Abraham Tr. 385:5-386:4. This point does not appear to be disputed. Defendants' expert Dr. McMillan agreed that short action could be due to at least either metabolism or excretion, if not also absorption and distribution. McMillen Tr. 494:12-22.

Green, PX 25, the principal reference upon which Defendants rely for pirenperone's alleged deficiencies, said nothing about the ketone in pirenperone. Abraham Tr. 384:15-22. Furthermore, it said nothing about pirenperone's metabolism. Abraham Tr. 384:19-22. From Green, nothing at all can be concluded about the reasons for pirenperone's alleged short duration. Abraham Tr. 385:5-8.

If pirenperone's alleged short duration was due to metabolism, it is

undisputed that it could metabolize at numerous places. Abraham Tr. 386:11-19, 387:14-20, 388:10-13; McMillen Tr. 495:19-496:14. Of the possible positions for metabolism, no position is more likely than any other. Abraham Tr. 388:14-20.

Mylan and DRL rely on the metabolism of other compounds to attempt to demonstrate the obviousness of pirenperone's alleged short activity. But none of the cited references provides the clear and convincing evidence Defendants need. For example, Defendants examine the metabolism of ketanserin and haloperidol to infer that pirenperone's ketone could be reduced to an alcohol and could result in a short acting compound. But there was no reason for one of skill in the art in 1985 to make that inference. As Dr. Wolff admitted, although the antipsychotic drug haloperidol and the hypertensive drug ketanserin had ketones that metabolized to an alcohol, they were both successful commercial products. Wolff Tr. 648:5-8, 652:20-653:3.

Moreover, although ketanserin metabolizes at the ketone to an alcohol, it is then metabolized back to the ketone, which makes ketanserin very long-acting. Abraham Tr. 390:23-391:9, 446:5-25; PX 174 at 342 ("In view of these results it is likely that the terminal ketanserin half-life of 15h is related to slow ketanserin regeneration from the metabolite ketanserin-ol.").

Similarly, Defendants rely on the Bachur article, PX 26, to contend that ketones metabolize. But Bachur does not predict which ketones are reduced to alcohols. It simply states that reduction to alcohols is a possibility. Abraham Tr. 389:4-8; PX 26. More importantly, Bachur emphasizes that when reduced to alcohols, most ketone-containing compounds usually retain pharmacological activity. Abraham Tr. 389:9-12, 389:22-390:2; PX 26 at 597 ("The alcohol metabolites resulting from carbonyl [ketone] reduction of drugs usually retain pharmacological activity."). Thus, after reading Bachur's conclusion that, if metabolized, drugs having ketones retain pharmacological activity, and considering the numerous successful drugs a person of ordinary skill in the art would be aware of that had ketones, that person would not conclude that pirenperone's ketone was necessarily a part of the molecule that needed to be removed or modified.

Taken as a whole, none of the cited references would convince the person of ordinary skill in the art that metabolism at the ketone was causing pirenperone to be short acting. For this reason as well, Mylan and DRL have failed to make out a clear and convincing case of obviousness.

d. Defendants' Solution to Pirenperone's Alleged Duration Problem Would Not Have Been Obvious to the Person of Ordinary Skill in the Art in 1985

A further flaw in Mylan and DRL's obviousness case is their proposed solution to pirenperone's alleged short-acting problem. If one of ordinary skill in the art wished to eliminate pirenperone's ketone to create a new, long-acting compound, that person would not have changed the ketone to a benzisoxazole.

(1) A Sustained Release Forumulation Would Have Been a More Obvious Solution

If there was a known problem with pirenperone's duration, one of ordinary skill in 1985 would have avoided modifying its chemical structure, because such modifications are risky and uncertain. It is undisputed that they can result in loss of efficacy or introduce safety issues. Wolff Tr. 650:8-13.

According to Defendants' expert Dr. Wolff, only three or four out of hundreds of modifications lead to a commercial product. Wolff Tr. 651:1-8. Dr. Wolff later described a reasonable expectation of success that a modification would result in a commercial product as on the order of five to 10 percent. Wolff Tr. 651:9-24. Even using Dr. Wolff's estimate, the expectation of success from structural modification was unreasonably low in 1985.[14]

[14] Cf. Abraham Tr. 374:3-8 ("Q. So what would a person of ordinary skill in the art expect to happen if they made one of these changes, would they expect to have a successful drug? A. There would be … no reasonable expectation you would come up with a drug using this method.").